REMARKS

Status of the Claims

Claims 1, 5, 10, 12, 14, 15, 8, 23, 25, 27-45, 47 and 48 are pending as shown above and claims 1, 5, 10, 12, 14, and 43-45 are under active examination. As the withdrawn method claims contain all the limitations of the examined composition claims, rejoinder of the method claims upon indication of allowable subject matter is in order.

Rejections Withdrawn

The previous rejections under 35 U.S.C. § 102(b) have been withdrawn. (Office Action, paragraph 1).

35 U.S.C. § 112, 1st paragraph

Claims 1, 5, 10, 12, 14, and 43-45 were again rejected under 35 U.S.C. § 112, 1st paragraph as not enabled throughout their scope by the as-filed specification. (Office Action, paragraph 2). It was alleged that it was unpredictable whether arginine phosphate and CHAPS would stabilize proteins other than LTK63. *Id.* The Examiner cited various references, including Wang et al. (1999), WO 01/41800 (Pike), Ryu et al. (1998), Strub et al. (2004) and Tsumoto et al. (2004), in support of the allegation that stabilization of proteins was unpredictable at the time of filing. *Id.* It was also alleged that the claims broadly encompass "analogs" and "other amino acids" that are not predictable. *Id.*

For the reasons of record and detailed below, Applicants submit that the specification fully enables the claims throughout their scope and that a *prima facie* case of non-enablement has not been established.

First and foremost, the Examiner has improper construed the pending claims. Contrary to the Examiner's assertions, the pending claims do not encompass "analogs" or "other amino acids" as stabilizing agents. Rather, the claims are clearly drawn to a composition comprising the following components: (1) a soluble, AB5 cholera toxin (CT) ADP-ribosylating toxin or an AB5 E. coli heat labile toxin (LT) protein; (2) arginine phosphate and (3) 3-(3-Cholamidopropyl)-dimethylammonio-1-propanesulfonate (CHAPS). There are no analogs or "other amino acids" recited in any of the pending claims.

Furthermore, the specification fully enables stabilization of either LT or CT proteins. As set forth in the seminal case of *In re Marzocchi,* 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971), a patent application is presumptively enabled when filed:

> [a]s a matter of Patent Office practice ... a specification .. must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Moreover,

> it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 369-370. Indeed, as pointed in the Patent Office's own Training Manual on Enablement (1993, citing *In re Wright,* 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

Thus, the relevant question regarding enablement remains what the specification and state of the art at the time of filing teaches one of skill in the art compositions comprising an LT or CT protein, arginine phosphate and CHAPS, as claimed.

It is admitted that the stabilization of the exemplified LTK63 protein can be reasonably extrapolated to LTK72 or native LT proteins. (Office Action, page 6). However, it was asserted that CT and LT are "completely different" proteins. *Id.*

Applicants note that this assertion is in error. In particular, as known to the skilled artisan and described in the art, CT and LT are virtually indistinguishable in terms of structure and function. Both are hexamers organized in the same way with an A subunit (containing 2 domains, one of which is toxic) surrounded by 5 B subunits and both are immunologically similar (page 13, line 8 to page 14, line 10; page 38 of the specification, emphasis added):

Preferred bacterial ADP-ribosylating exotoxins (bAREs) for use in the compositions of the present invention include cholera toxin (CT) and the E. Coli heat labile toxin (LT). The CT and LT exotoxins are hexamers, composed of a single molecule of an A subunit surrounded by a doughnut-shaped ring composed of 5 molecules of the B subunit. The heat-labile toxin (LT) of enterotoxigenic E. Coli (ETEC) is structurally, functionally and immunologically similar to CT and the two toxins cross-react immunologically. Conventionally, CT and LT proteins are termed AB5 proteins. The entire native protein is indicated as AB5, the partly dissociated subunits as A and B5 pentameric form consisting of five identical subunits and the single monomer of the B subunit designated as Bm.

CT is the prototype bacterial enterotoxin. It is a protein built from two types of subunits: a single A subunit of molecular weight 28,000 and five B subunits, each with a molecular weight of 11,600 giving a holotoxin with approx 84,000 molecular weight. The B subunits are aggregated in a ring by tight noncovalent bonds; the A subunit is linked to and probably partially inserted in the B pentamer ring through weaker noncovalent interactions. The two types of subunits have different roles in the intoxication process: the B subunits are responsible for cell binding and the A subunit for the direct toxic activity. The A subunit contains two domains. The A1 domain possesses ADP-ribosylating activity, which is responsible for the toxicity of the A subunit. The A2 domain interacts with the B oligomer. The enzymatic activity requires the proteolytic cleavage of the loop between the two domains and the reduction of the disulfide bridge between A1-cys187 and A2-cys199. The toxic A subunit induces the enzymatic changes (due to its ADP-ribosylating activity) which lead to fluid secretion and diarrhoea while the non-toxic B subunit is the immunogenic moiety that binds to the GM-1 ganglioside receptor for the toxin on intestinal epithelial cells (Holmgren J Nature (1981) 292; 413).

LT is a type I Escherichia coli heat-labile enterotoxin. It consists of (i) an A subunit composed of a single polypeptide chain of 240 amino acids with a molecular weight of around 27 kDa, which contains the toxic ADP-ribosylating activity and (ii) a pentameric ring-shape B5 complex formed by five identical monomers of 103 amino acids each with a molecular weight of around 58.5 Da which contains the ganglioside binding sites. The internal side of the B5 pore is composed of charged amino acids that interact with the A2 domain of the A subunit, corresponding to the amino acids 193-240. The rest of the A subunit, A1 domain, retains the catalytic activity. Both the A and B subunits contain a high percentage of positively charged amino acids (subunit A, IP=6.3, Subunit B, IP=8.87 and AB5, IP=8.5).

It is well known in the art that cholera toxin (CT) and the related E. Coli heat labile enterotoxins (LT), which are secretion products of their respective enterotoxic bacterial strains, are potent immunogens and exhibit strong toxicity when administered systemically, orally, or mucosally. In addition, it is well

> known that CT and LT can provide adjuvant effects for antigen when administered via the intramuscular or oral routes. The two toxins are **extremely similar** molecules, and are at least about 70-80% homologous at the amino acid level.

In addition to teaching that LT and CT are structurally and functionally extremely similar, the specification clearly teaches what was known to the skilled artisan, namely that LTK63 is but one example of an LT or CT protein that retains the structure of wild-type LT and CT (Example 1 of the as-filed specification, emphasis added):

> LTK63, an oligomeric protein of about 82 KDa, is a non-toxic mutant of LT (heat-labile enterotoxin), obtained by site specific mutagenesis on subunit A that retains the structural organization of the native molecule. LTK63 subunit A is composed by a single polypeptidic chain of 240 amino acids, with a MW of 27 KDa. Subunit B is a pentamer formed by 5 identical monomers of 103 amino acids each, with a MW of 55 KDa. Both subunits contain high percent of positive charged amino acids (subunit A IP=6.3; subunit B_5, IP=9.1; integral AB_5 IP=8.5).

Thus, the presumptively enabling specification clearly supports the interchangeability of LT and CT proteins.

Furthermore, the Examiner has not presented evidence which backs up the assertions that LT and CT are not considered to be structurally and functionally similar. In particular, none of the references cited in the Office Action provide a properly reasoned and supported basis for finding non-enablement.

Wang, which was cited for allegedly demonstrating the "unpredictability" of stabilizing proteins, is not germane to the pending claims. Wang was published 4 years prior the effective filing date of the instant application and is not indicative of the state of the art at the time of filing. Nor has the Examiner indicated where Wang in any way addresses stabilization of LT or CT proteins as claimed. Likewise, Pike was published in 1990, fully 13 years prior to the effective filing date of the instant application and, like Wang, does not address LT or CT proteins *per se*. Accordingly, Wang and Pike do not establish non-enablement of the claims at issue.

Tsumoto, Ryu and Strub were also cited for allegedly demonstrating that protein stabilization was, at the time of filing, unpredictable. However, these references are in no way

concerned with LT or CT proteins and, accordingly, do not in any way establish unpredictability of the claimed subject matter.

Therefore, as the cited references are not relevant to the pending claims, the Examiner errs in asserting exemplary experiments with LTK63 are not predictive of LT and CT proteins generally. The fact remains that the skilled artisan reading the specification would know that any LT or CT protein would behave similarly in the context of stabilization in light of the fact that they are extremely similar proteins. While different classes of proteins may behave differently in regards to stabilization, the Examiner has not presented any evidence that establishes CT and LT proteins (and/or recombinant mutants of these proteins that retain the structural organization of the wild-type proteins) would be expected to behave differently. To the contrary, the specification and state of the art clearly establishes that the skilled artisan considered LT and CT proteins to be interchangeable, not different.

Applicants also traverse the Examiner assertions that the as-filed specification teaches unpredictability of the claimed compositions (see, pages 4-5 and 7 of the Office Action, underlining in original):

> The specification at page 21 teaches that there are some conflicting reports on the benefits of an amorphous excipient in terms of stabilization and that some studies have shown that the addition of an amphorous excipient to protein solutions can actually destablise a protein through interactions between the excipient and the protein [citing Pike]. ... The specification at the bottom of page 24 teaches that identification of Arginine as a stabilizing agent is unexpected.
>
> The top of page 81 of the instant specification teaches that CHAPS and L-arginine were selected to synergistically stabilize the LT K63 protein, e.g., by preventing both precipitation and dissociation over time. It is noted that one would not use a non-mutant LT or CT toxin in an 'immunogenic composition' as claimed in instant claims 43-45.

Again, the claims are not drawn to amorphous excipients for general proteins as discussed in Pike. Rather, the claims are drawn to compositions comprising LT or CT, CHAPS and arginine phosphate. It is shown in the specification that CHAPS and arginine phosphate stabilize LT or CT proteins, therefore it is clear that Pike is not relevant as the claimed compositions are not destabilized by the particular combination of claimed elements. Furthermore, the reference to page 24 of the specification stating that "the identification of

Arginine as a stabilizing agent is unexpected" does not in any support a finding of non-enablement. It simply sets forth what is fully enabled by the as-filed specification (as well as novel and inventive), namely compositions as claimed comprising LT or CT, CHAPS and arginine phosphate.

Turning to the Examiner's citation to page 81 of the specification, Applicants note that Example 9 regarding stability LTK63 in CHAPS and arginine phosphate over time is but one example of the claimed compositions. Moreover, the assertion that non-mutant LT or CT proteins would not be used in immunogenic compositions is in error. As noted above (for example on page 38 of the specification, reproduced above), it was well known at the time of filing that non-mutant LT or CT proteins are potent immunogens and/or adjuvants.

Simply put, there is ample disclosure in the as-filed specification to allow the skilled artisan to make and use stabilized LT or CT compositions as claimed. Exemplification of multiple LT or CT proteins not required to show enablement of the pending claims, as such these proteins were considered to be so similar as to be virtually identical by the skilled artisan. Indeed, it is well settled that even time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.,* PTO Training Manual on Enablement, pages 30-31, citing *United States v. Telectronics Inc.,* USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). Thus, in the instant case, Applicants are not required to actually have exemplified CT proteins – the disclosure is more than ample to allow the skilled artisan to make and the use the claimed compositions for either CT or LT without undue experimentation.

Finally, in view of the clear guidance of the specification, the facts and holding in *Genentech v. Novo Nordisk* are inapposite to the pending case. In *Genentech,* the specification lacked "reasonable detail" regarding what is novel, whereas in the pending case there are pages of disclosure as to what is new, namely using CHAPS and arginine phosphate to stabilize LT or CT proteins. *Genentech* did not require the reiteration of known aspects, but rather that the novel aspects are supplied by the as-filed specification. Here, the novel aspect of using CHAPS and arginine phosphate to stabilize LT or CT proteins is fully enabled.

Thus, the Office has not provided sufficient evidence supporting non-enablement and, in the absence of necessary relevant evidence contradicting the teachings of the specification and state of the art, the rejection cannot be maintained.

CONCLUSION

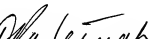
In view of the foregoing, Applicants submit that the claims are in condition for allowance.

Please direct all further communications regarding this application to:

Helen Lee
NOVARTIS VACCINES AND DIAGNOSTICS, INC.
Intellectual Property – X100B
P. O. Box 8097
Emeryville, CA 94662-8097
Customer No: 27476

Respectfully submitted,

Date: June 21, 2010

By: 
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicant

NOVARTIS VACCINES AND DIAGNOSTICS, INC.
Intellectual Property – X100B
P. O. Box 8097
Emeryville, CA 94662-8097
Tel.: (650) 493-3400
Fax: (650) 493-3440